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(57) Abstract

The invention provides a composition useful as a pharmaceutical excipient, the method of producing same, and the pharmaceutical compositions obtained thereby. In particular, the invention has applicability to increasing the solubility of poorly soluble therapeutically active compounds, by means of an excipient comprising a mixture of: (a) saturated polyglycolyzed glycerides, and (b) polyoxypropylene–polyoxyethylene block copolymers, whereby the solubility of the poorly soluble therapeutically active compound in the pharmaceutical composition is enhanced.

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SOLID STATE SOLUTIONS AND DISPERSIONS OF POORLY WATER SOLUBLE DRUGS

Field of the Invention

This invention relates to a composition especially useful as a pharmaceutical solutibility excipient, the method of producing same, and the pharmaceutical compositions obtained thereby. In particular, the invention has applicability to increasing the solubility of poorly soluble therapeutically active compounds.

Summary of the Invention

The invention provides a pharmaceutical solubility enhancing excipient for a pharmaceutical composition comprising a poorly water soluble therapeutically active compound, said excipient comprising a mixture of:

(a) saturated or unsaturated polyglycolyzed glycerides, and

(b) polyoxypropylene-polyoxyethylene block copolymers,

The invention further provides a pharmaceutical composition comprising a solid state solution or solid state dispersion of a poorly water soluble therapeutically active compound and a pharmaceutically acceptable excipient, said excipient comprising a mixture of:

(a) saturated or unsaturated polyglycolyzed glycerides, and

(b) polyoxypropylene-polyoxyethylene block copolymers,

whereby the solubility of the poorly soluble therapeutically active compound in the pharmaceutical composition is enhanced.

The invention further provides methods for making the above compositions. In the first instance (a) and (b) are mixed to form an excipient mixture. In the second instance, to form a pharmaceutical composition, heating said polyglycolyzed glycerides and polyoxypropylene-polyoxyethylene block co-polymer sufficiently to melt the ingredients,

adding the therapeutic agent to the molten mixture of polyglycolyzed glycerides and polyoxypropylene-polyoxyethylene block co-polymer

maintaining the mixture at a sufficient temperature for a sufficient time to dissolve or disperse the pharmaceutical agent.

The method aspect of the invention further comprises adding one or more optional excipients, whereby:

(A) the solubility of the therapeutically-active compound in the polyglycolyzed glyceride:polyoxypropylene-polyoxyethylene block co-polymer mixture is increased, or

(B) the melting point of the non-drug components is set, whereby at least one melting point peak belonging to the non-drug components is present between 30-80°C in the final composition, when analyzed by thermal analytical techniques.

The method aspect of the invention further comprises

maintaining the resulting mixture in the molten form, with constant stirring to ensure homogenous distribution of the drug in the system, and then

subjecting the molten mixture to one or more of the following operations:

I) allowing the mixture to congeal to a solid mass, and then extruding the mixture through a hot melt extruder into a powder;

II) milling the mixture using equipment that would maintain the milling conditions at room temperature or below the melting point of the non-drug components of the system to enable milling the composition into a powder;

III) spray-congealing the mixture in a spray drier or fluidized bed drier to a powder;

IV) congealing the mixture onto one or more optional excipients in a spray drier, fluidized bed drier, rotor, high shear granulator, planetary mixer, blender, or any conventional food and pharmaceutical processing equipment;

V) formulating the above-mentioned powders in pharmaceutical tablets, capsules, powders for inhalation, suppositories, suspensions, and emulsions; or

VI) congealing said mixture onto a solid pharmaceutical tablet, capsule or granule.

It has been discovered that by utilizing a mixture of: (a) saturated or unsaturated polyglycolyzed glycerides, as exemplified by the commercial Gelucire compositions and (b) polyoxypropylene-polyoxyethylene block copolymers, as exemplified by the commercial Pluronic surfactants, it is possible to prepare solid state solutions or solid state dispersions containing poorly soluble therapeutically active compounds, which compositions, in turn, provide a high degree of solubility to the therapeutic agent.

Gelucires are polyglycolyzed glycerides prepared by the alcoholysis reaction of natural oils with polyoxyethylene glycols. They are mixtures of monoesters, diesters and/or triesters of glycerides of long chain C_{12} to C_{18} fatty acids, and in polyethylene glycol mono- and/or diesters of long chain fatty acids. These preparations have a wide range of melting points of from about 33°C to 64°C, as well as a wide range of hydrophilic/lipophilic balance values (HLB) from about 1 to about 14. The Gelucires of particular interest in the present invention have an HLB of above 10.

The first number in the nomenclature of a Gelucire denotes its melting point, whereas the second number provide the HLB value. The preferred Gelucires of the present invention are grades 44/13 and 50/13.

The Pluronic surfactants are block copolymers of polyoxyethylene and polyoxypropylene, generally having an average molecular weight from about 3,000 to about 15,000. The ethoxylated portion of the blocked copolymer generally constitutes from about 30 to about 80% by weight of the molecule. Particularly good results are achievable with Pluronic F68, F108 and F127, but in any case, it is to be noted that the Pluronic constituent should also have an HLB above 10, irrespective of the particular grade which is selected. For example, Pluronic F108 has an average molecular weight of 14,600, a polyoxyethylene content of about 80 weight % and an HLB value in excess of 24, and Pluronic F127 has an average molecular weight of 12,600, a polyoxyethylene content of about 70 weight % and an HLB value from 18 to 23.

The weight ratio of the combined saturated polyglycolyzed glycerides: polyoxypropylene-polyoxyethylene block co-polymer generally range between 0.10-99.9 to 99.9:0.10, with preferred ratios being 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. These combinations especially the 5:5 ratio, yields a mixture having a melting point in the range of 44-70°C, preferably 50°C-70°C.

The composition of saturated polyglycolized glyceride and polyglyoxypropylene-block copolymer is combined with a therapeutic agent, wherein said composition is present in the final composition, the latter including the therapeutic agent, in a range of about 0.10-99.9% by weight, with the preferred range being 5-75% by weight of the final composition. Poorly soluble agents, e.g., therapeutic agents which have an intrinsic water solubility of less than 10.0 g/l are particularly benefitted by the present invention. Examples of drugs in this category are drugs belonging to the dihydropyridine class of compounds (e.g., nifedepine, felodipine, nicardipine), omperazole, spironolactone, furosemide, terbutaline, riboflavine, gemfibrozil, indomethacin, ibuprofen, phenytoin, glyburide. In addition, any drug which has a water solubility of less than 10.0 g/l belonging to, for example, cardiovascular, cholesterol lowering, anti-hypertensive, antiepileptic, hormonal, hypoglycemic, antiviral, immunosuppressive, antihistaminic, nasal decongestant, antimicrobial, antiarrthrytic, analgesic, antimycobacterial, anticancer, diuretic, antifungal, antiparasitic, protein, peptide, CNS stimulants, CNS depressants, 5-HT inhibitors, anti-schizophrenia, anti-Alzheimer, antipsoriatic, steroidal, oligonucleotide, antiulcer, proton pump inhibitor, anti asthmatic, bronchodialators, thrombolytics, vitamin class of therapeutic agents, any combinations thereof may be used in this composition in order to form solid state solutions and dispersions.

The final composition optionally comprises the following further excipients at 5-95%, especially 10-70% by weight of the final composition. Examples of the further excipients include, but are not limited to ascorbyl palmitate, glycerol, glyceryl monooleate, glyceryl monosterate, glyceryl palmitosterate, triglycerides, diglycerides, monoglycerides, diesters of PEG, monoesters of PEG, polyethylene glycol, glycery polyoxyethlene fatty acid esters, glyceryl polyoxyethylene polyethylene glycol fatty acid esters and ethers, polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sterates, polyvinyl alcohol, sorbitan fatty acid esters, polyoxyl sterates, polyethylene glycol

hydroxysterate, polyoxyethylene alcohols, anionic, cationic, amphiphillic compounds, carbohydrates (lactose, maltodextrins, sucrose, starch, etc.), polyols (sorbitol, mannitol, xylitol, etc.), microcrystalline cellulose, vitamins (ascorbic acid, niacinamide, etc.), and inorganic compounds (calcium carbonate, dicalcium phosphate), polyoxyethylene castor oil derivatives, propylene carbonate, anionic emulsifying wax, white wax, yellow wax, hydrogenated vegetable oil, triacetin, triethyl citrate and other plasticizers (food and pharmaceutical grade), lecithin, phospholipids, soybean oil, sesame oil, cotton seed oil, sunflower oil, peanut oil, mineral oil, hydrogenated castor oil, water soluble and insoluble derivatives of cellulose (e.g. ethyl cellulose, methyl cellulose, HPMC, HPC, cellulose acetate phthalate, etc.), methacrylates and polymethacrylates (e.g., Eudragit®), canola oil, benzoic acid and its salts, methyl-, propyl- and butyl-para-amino benzoic acid (paraben) (preservatives), organic acids (e.g., fumaric, adipic, maleic, etc.), ethyl alcohol, saccharine, cyclamate sodium, and other artificial sweeteners, food and pharmaceutical flavoring agents, bioflavanoids (e.g., quercetin, isoquercetin), citrus bioflavanoids (e.g., naringin), citrus bioflavanoid complexes, and other agents that inhibit the enzyme cytochrome P450 4A4 (also called as CYP3A4), galactose oligosaccharides (example of a functional carbohydrate), lubricant (e.g. magnesium sterate), anti-caking agent (e.g., silicon dioxide, sodium aluminum silicate, magnesium trisilicate, talc, etc.), gums (locust bean gum, gum arabic, arabinogalactan, etc.); and any combination of said excipients.

To enhance the solubility of the therapeutically active agent, an aspect of this invention provides that the composition of the therapeutic reactive agent, the polyglycolyzed glyceride and the polyoxypropylene-polyoxyethylene block co-polymer is formed into a solid state solution or solid state dispersion.

A solid state solution is defined as a solution of the drug in a solid form. A solid state solution of a drug is characterized by the lack of a melting point peak at the melting point of the drug indicating the absence of the solid state of the drug. A solid state solution-dispersion is defined as a system in which part of the system may be in the solid solution form and part of it may be in the form of a finely dispersed solid form in the system. This solid state solution - dispersion is further defined as a system in which more than 1% of the total drug content can exist as a solid solution and more than 1% of the drug can exist as a solid dispersion with a particle size distribution such that 90% of the

particles have a diameter less than 10 microns. The weight ratio between the solid state solubilized drug: dispersed drug may be in the range of 1.0-100:99-0. It is desirable that 30-100% of the drug exists as a solid state solution. The ratio of the amount of drug present in the form of a solid state solution to the amount present as a solid dispersion is easily ascertained by the use of techniques in thermal analysis such as Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA), and Differential Scanning Microcalorimetry. The crystallinity of the drug is easily determined by X-ray diffraction. Furthermore, when determined by thermal analytical techniques it is desirable that the final composition have at least "one" distinct melting peak in the range of 30-80°C associated with the melting point of the non-drug components of the final composition.

To produce the final composition polyglycolyzed glycerides and polyoxypropylene-polyoxyethylene block co-polymer are heated sufficiently to form a melt of the ingredients, for example to at least about 20°C above the combined melting point. The therapeutic agent is added gradually to the molten mixture of polyglycolyzed glycerides and polyoxypropylene-polyoxyethylene block co-polymer. It is preferable to mill or micronize the drug to a particle size range such that the particle diameter of 90% of the particles is less than 75 microns. The mixture is maintained at a sufficient temperature, for example, at least about 20°C above the combined melting point of the polyglycolyzed glycerides: polyoxypropylene-polyoxyethylene block co-polymer mixture for a sufficient time to dissolve or disperse the pharmaceutical agent.

The optional excipients may be added to the above mentioned system to,

(A) Increase the solubility of the drug in the polyglycolyzed glycerides: polyoxypropylene-polyoxyethylene block co-polymer system.

(B) Set the melting point of the non-drug components, such that at least "one" melting point peak belonging to the non-drug components is present between 30-80°C in the final composition, when analyzed by thermal analytical techniques.

The resulting mixture is then maintained in the molten form, for example, at least 20°C above the combined melting point of the non-drug components, with constant

stirring to ensure homogenous distribution of the drug in the system. Thereafter, the mixture may be subjected to one or more of the following operations:

I) Allowed to congeal to a solid mass, and then extruded through a hot melt extruder into a powder.

II) Milled using equipment that would maintain the milling conditions at room temperature or below the melting point of the non drug components of the system to enable milling the composition into a powder.

III) Spray congealed in a spray drier or fluidized bed drier to a powder.

IV) Congealed onto one or more of said excipients in a spray drier, fluidized bed drier, rotor, high shear granulator, planetary mixer, blender, or any conventional food and pharmaceutical processing equipment.

V) The above mentioned powders may then be used in the formulation of conventional, specialized, and novel pharmaceutical dosage forms such as tablets, capsules, powders for inhalation, suppositories, suspensions, and emulsions.

VI) Alternatively, the molten mixture can be congealed into or onto a solid pharmaceutical dosage form such as, for example, a tablet, capsule, and/or granule.

The entire disclosure of all applications, patents and publications, cited above and below, and also U.S. provisional application 60/063,338 filed October 27, 1997 are hereby incorporated by reference.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

EXAMPLES

Example 1:

Three grams of Gelucire of 50/13 and 3 grams of Pluronic F68 are melted and two grams of nifedipine are dissolved therein. The resultant solution is added to 4 grams of sorbitol while stirring. The resultant solution is then cooled down and passed through a 20 mesh screen. The resultant particulate solids were solid solutions.

Example 2:

In this example, felodipine is employed as the active pharmaceutical agent. Thus, 1.5 grams of Gelucire 50/13 and 1.5 grams of Pluronic F68 were melted together and 1 gram of felodipine was added thereto. This resultant solution was then introduced into 4 grams of Sorbitol P300® while stirring. After mixing, the solution was cooled and ultimately passed through a 20 mesh screen. The resultant particulate solids were in a solid state solution-dispersion system.

Example 3:

In this example, felodipine is employed as the active pharmaceutical agent. Thus, 1.5 grams of Gelucire 50/13 and 1.5 grams of Pluronic F68 were melted together and 1.5 grams of felodipine was added thereto. This resultant solution was then introduced into 4 grams of Sorbitol P300® while stirring. After mixing, the solution was cooled and ultimately passed through a 20 mesh screen. The resultant particulate solids were in a solid state solution system.

Example 4:

In this example, felodipine is employed as the active pharmaceutical agent. Thus, 1 gram of Gelucire 50/13 and 1 gram of Pluronic F68 were melted together and 1.5 grams of felodipine was admixed. This resultant solution was then added to 2.67 grams of Avecil, a brand of microcrystalline cellulose. After mixing, the solution was cooled and ultimately passed through a 20 mesh screen. The resultant particulate solids were in a solid state solution-dispersion system.

For the purposes of increasing the melting point of the composition of Examples 2, 3 and 4, Pluronic F127 can be substituted for Pluronic F68.

To determine the improvement achieved by the present invention with respect to the solubility of pure felodipine, the formulations of Examples 3 and 4 were evaluated by the following technique.

The solubility characteristics of the compositions of Examples 3 and 4 as compared to pure felodipine were evaluated, as follows:

- 6.8 mg of felodipine and 34.8 mg of the composition of Example 3 and 34.2 Example 4 are respectively placed into 500 ml of a 40% PEG solution maintained at 37°C.

The solution was stirred with a paddle stirrer at 50 rpm. The absorbency was measured with a Hitachi spectrometer at 362 nm. The percent release is based on the standard curve: absorbents = 0.216 conc. (mg/900 ml)-0.00274, and the following results were obtained.

Percent released (%)			
Time (h)	Pure felodipine	Example 3	Example 4
0.5	9.2	62.4	65.6
1	21.1	76.4	78
2	49.5	84.4	84.6
3	66.8	85.7	86.3

From the above table, it is clear that the present invention provides a substantially enhanced solubility as compared to the pure drug.

Example 5:

For the production of tablets 121.5 mg of HPMC (hydropropylmethyl cellulose) are mixed with 21.1 gm of Sorbitol Instant P300®, 246.88 mg of Microcrystalline Cellulose and 59.62 mg of the composition of Example 3. 1 mg of magnesium stearate was then added to the above mixture with stirring. The resultant mixture was tableted in a Carver® press under a pressure of 2 tons.

Example 6:

Another tablet was produced from the composition of Example 3 by the method of Example 5 except in this case, the amount of Example 3 was 59.52 mg, Microcrystalline Cellulose 231.98 mg, Sorbitol Instant P300® 45 mg and HPMC 112.5 mg, with sodium stearyl fumerate (PRUV)® being substituted for magnesium stearate.

The resultant tablet has 10% sorbitol.

Example 7:

In this example, a 15% sorbitol tablet is produced in the same manner as the last example except that the amount of sorbitol is 67.5 mg and the amount of Microcrystalline Cellulose is 209.48 mg.

Example 8: Intrinsic Dissolution of Hydrosolve-Ibuprofen

a. Formulation:

Excipient	Quantities (g)	Supplier
Ibuprofen	2.5	Albermarle
Pluronic F68	2	BASF
Gelucire 50/13	0.5	Gatterfosse
Sorbitol Instant P300	5	EM Industries

b. Procedures:

1.Melt Gelucire and Pluronic, and dissolve ibuprofen into the mixture.

2.Add the above solution into Sorbitol Instant while stirring.

3.Cool down and pass through #20 mesh screen.

c. Dissolution Test Using the Dissolution Test as follows:

1.Measure 3.3 mg and 17.2 mg of ibuprofen (20 micron) and HydroSolve - Ibuprofen, respectively.

2.Measure the dissolution profiles using 700 ml of pH 7.2 buffer and paddle at 50 rpm.

3.Measure the absorbance at 221 nm.

Results:

Time(min)	Ibuprofen	HydroSolve
10	75.93	85.19
20	81.14	95.28
30	81.14	99.07

Example 9: Intrinsic Dissolution Profile of Phenytoin and HydroSolve- Phenytoin

a. Formulation #4:

Excipient	Quantities (g)	Supplier
Phenytoin	1	Spectrum Quality Products
Gelucire 50/13	1	Gattefosse
Pluronic F68	1	BASF

b. Procedures:

1. Melt Gelucire and Pluronic together.
2. Dissolve the phenytoin into above solution.
3. Congeal this suspension and pass through #20 mesh.
4. Measure about 32 and 110 mg of phenytoin and HydroSolve - phenytoin, respectively.
5. Measure the dissolution profiles using 900 ml of D1 water and Paddle Method at 50 rpm.
6. Using D1 water as blank, measure the absorbance at 220 nm of each sample which is filtered through 0.45 micron filters.
7. Calculate the percent released by standard curve:

   Absorbance = 0.4072 x Concentration (mg/100ml) + 0.0227

c. Results:

	% Dissolved (%)	
Time (h)	Phenytoin	HydroSolve
0.5	3.03	60.67
1	5.92	67.27
2	14.42	72
3	20.58	73.38

Example 10: The DSC Profiles for HydroSolve System of Phenytoin

1a. Formulation #1:

Excipient	Quantities (g)	Supplier
Phenytoin	1	Spectrum Quality Products
Gelucire 50/13	1	Gatterfosse
Pluronic F68	1	BASF
Sorbitol Instant P300	2.5	EM Industries

2b. Procedures:

1.Melt Gelucire and Pluronic together.

2.Disperse the phenytoin into above solution since pheytoin cannot completely.

3.Mix the above suspension with sorbitol P300 while stirring.

4. Measure the DSC profile.

2a. Formulation #4:

Excipient	Quantities (g)	Supplier
Phenytoin	1	Spectrum Quality Products
Gelucire 50/13	1	Gatterfosse
Pluronic F68	1	BASF

2b. Procedures:

1.Melt Gelucire and Pluronic together.

2.Dissolve/disperse the phenytoin into above system.

3.Congeal this suspension and pass through #20 mesh.

4. Measure the DSC profile.

c. Results:

	PEAKS	
Material	Endotherm (°C)	Exotherm (°C)
Phenytoin:	298.5	
Pluronic F68:	56.6	163.4
F#1:	52.3	179.2
F#4:	52.4	174.2

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

1. A pharmaceutical excipient suitable as a solubility enhancer for a pharmaceutical composition comprising a poorly water soluble therapeutically active compound, said excipient comprising a mixture of:

(a) polyglycolyzed glycerides, and

(b) polyoxypropylene-polyoxyethylene block copolymers.

2. An excipient of claim 1, wherein (a) is a Gelucire composition.

3. An excipient of claim 1, wherein (b) is a Pluronic surfactant.

4. An excipient of claim 1, wherein (a) is a Gelucire composition wherein the composition of the C_{8-18}-long-chain fatty acids in the glycerides comprises <10% C_8-fatty acid, <10% C_{10}-fatty acid, <50% C_{12}-fatty acid, <25% C_{14}-fatty acid, <50% C_{16}-fatty acid, and <58% C_{18}-fatty acid.

5. An excipient of claim 1, wherein (a) is a Gelucire composition wherein the composition of the C_{8-18}-long-chain fatty acids in the glycerides comprises at least one of polyethylene glycol mono- or diesters of said fatty acids.

6. An excipient of claim 4, wherein (a) is a Gelucire composition wherein the composition of the C_{8-18}-long-chain fatty acids in the glycerides comprises at least one of polyethylene glycol mono- and diesters of said fatty acids.

7. A pharmaceutical composition comprising a solid state solution or solid state dispersion of a poorly water soluble therapeutically active compound and a pharmaceutically acceptable excipient, said excipient comprising a mixture of:

(a) polyglycolyzed glycerides, and

(b) polyoxypropylene-polyoxyethylene block copolymers,

whereby the solubility of the poorly soluble therapeutically active compound in the pharmaceutical composition is enhanced.

8. A pharmaceutical composition of claim 7, wherein (a) is a Gelucire composition.

9. A pharmaceutical composition of claim 7, wherein (b) is a Pluronic surfactant.

10. A pharmaceutical composition of claim 7, wherein (a) is a Gelucire composition wherein the composition of the C_{8-18}-long-chain fatty acids in the glycerides comprises <10% C_8-fatty acid, <10% C_{10}-fatty acid, <50% C_{12}-fatty acid, <25% C_{14}-fatty acid, <50% C_{16}-fatty acid, and <58% C_{18}-fatty acid.

11. A pharmaceutical composition of claim 7, wherein (a) is a Gelucire composition wherein the composition of the C_{8-18}-long-chain fatty acids in the glycerides comprises at least one of polyethylene glycol mono- and diesters of said fatty acids.

12. A pharmaceutical composition of claim 10, wherein (a) is a Gelucire composition wherein the composition of the C_{8-18}-long-chain fatty acids in the glycerides comprises at least one of polyethylene glycol mono- and diesters of said fatty acids.

13. A pharmaceutical composition of claim 7, wherein the composition comprising the solid state solution or solid state dispersion of a poorly water soluble therapeutically active compound and the excipient is granulated, pelleted, extruded, extrusion spheronized, or spray congealed.

14. A pharmaceutical composition of claim 7, wherein the composition comprising the solid state solution or solid state dispersion of a poorly water soluble

therapeutically active compound and the excipient is combined with an agent that modifies the release profile of the therapeutically active compound.

15. A pharmaceutical composition of claim 14, wherein the agent that modifies the release profile of the therapeutically active compound is a polymer of cellulose or a derivative thereof, alginic acid or a derivative thereof, polyvinyl alcohol or a derivative thereof, acrylic acid polymer, polymethacrylates, acrylic acid or a derivative thereof, lactic acid or a derivative thereof or gelatin.

16. A pharmaceutical composition of claim 14, wherein the composition comprising the solid state solution or solid state dispersion of a poorly water soluble therapeutically active compound and the excipient is in the form of a granule, particle, pellet, tablet or sphere, and is coated with the agent that modifies the release profile of the therapeutically active compound.

17. A method for manufacturing an excipient for a pharmaceutical composition, said composition comprising a solid state solution or solid state dispersion of a poorly water soluble therapeutically active compound, said excipient comprising a mixture of:

(a) polyglycolyzed glycerides, and

(b) polyoxypropylene-polyoxyethylene block copolymers,

whereby the solubility of the poorly soluble therapeutically active compound in the pharmaceutical composition is enhanced, comprising:

heating said polyglycolyzed glycerides and polyoxypropylene-polyoxyethylene block co-polymer sufficiently to melt the ingredients,

adding the therapeutic agent to the molten mixture of polyglycolyzed glycerides and polyoxypropylene-polyoxyethylene block co-polymer

maintaining the mixture at a sufficient temperature for a sufficient time to dissolve or disperse the pharmaceutical agent.

18. A method of claim 17, further comprising adding one or more optional excipient, whereby:

(A) the solubility of the therapeutically-active compound in the polyglycolyzed glyceride:polyoxypropylene-polyoxyethylene block co-polymer mixture is increased, or

(B) the melting point of the non-drug components is set, whereby at least one melting point peak belonging to the non-drug components is present between 30-80°C in the final composition, when analyzed by thermal analytical techniques.

19. A method of claim 17, further comprising

maintaining the resulting mixture in the molten form, with constant stirring to ensure homogenous distribution of the drug in the system, and then

subjecting the molten mixture to one or more of the following operations:

I) allowing the mixture to congeal to a solid mass, and then extruding the mixture through a hot melt extruder into a powder;

II) milling the mixture using equipment that would maintain the milling conditions at room temperature or below the melting point of the non-drug components of the system to enable milling the composition into a powder;

III) spray-congealing the mixture in a spray drier or fluidized bed drier to a powder;

IV) congealing the mixture onto one or more optional excipients in a spray drier, fluidized bed drier, rotor, high shear granulator, planetary mixer, blender, or any conventional food and pharmaceutical processing equipment;

V) formulating the above-mentioned powders in pharmaceutical tablets, capsules, powders for inhalation, suppositories, suspensions, and emulsions; or

VI) congealing said mixture onto a solid pharmaceutical tablet, capsule or granule.

20. A pharmaceutical composition according to claim 7 in the form of a solid state solution.

21. A pharmaceutical composition according to claim 7 in the form of a solid state dispersion.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/EP 98/06544

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAES, P. ET AL: "In vitro and in vivo behavior of some liquid or semi-solid filled hard gelatin capsules" BULL. TECH./GATTEFOSSE REP. (1996), 89, 63-70 CODEN: BTGRDQ;ISSN: 0397-7617, XP002099025 see page 67 ---	1-13,17, 20,21
A	DORDUNOO, S. K. ET AL: "Preformulation studies on solid dispersions containin triamterene or temazepam in polyethylene glycols or gelucire 44/14 for liquid filling of hard gelatin capsules" DRUG DEV. IND. PHARM. (1991), 17(12), 1685-713 CODEN: DDIPD8;ISSN: 0363-9045, XP002099026 see page 1689 - page 1690 ---	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 1999	16/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 98/06544

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 43635 A (GAUTIER JEAN CLAUDE ;SANOFI SA (FR); MARRIER JEAN MARIE (FR)) 8 October 1998 see page 3, line 9 - page 4, line 5 ---	1-13,17, 20,21
X	WO 96 21439 A (GALEPHAR P R INC ;DEBOECK ARTHUR M (PR); BAUDIER PHILIPPE (BE); MA) 18 July 1996 see page 9; example 1 ---	1-12,17, 19-21
X	US 5 487 887 A (BENFATTO ANTHONY) 30 January 1996 see column 9; example 5 ---	1-6
A	GINES, J. M. ET AL: "Elaboration and thermal study of interactions between cinnarizine and Gelucire 53/10 physical mixtures and solid dispersions" INT. J. PHARM. (1995), 126(1,2), 287-91 CODEN: IJPHDE;ISSN: 0378-5173, XP002099028 see the whole document -----	1-21

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 98/06544

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		AU 7052698 A	22-10-1998
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US 5487887 A	30-01-1996	US 5575990 A	19-11-1996